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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,664	08/22/2003	Ben Shen	054030-0031	3619

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,664	SHEN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-18 and 21-25 in the response filed January 31, 2006 is acknowledged. The traversal is on the ground(s) that all three groups are classified in the class and subclass, and all these claims have common materials (i.e., SEQ ID NO:2, 3, 4 and 5), thus the search and examination of entire application can be made without serious burden. The response has been considered, however, the argument is not found persuasive because co-examination of Groups II-III would require additional search for the catalytic domain of hybrid enzyme or megasynthetase, which are unnecessary for the examination of the elected claims. Therefore, co-examination of each of these inventions would require a serious additional burden of search.

The restriction groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the invention is not coextensive particularly with regard to the literature search. A reference which would anticipate the invention of one group would not necessarily anticipate or make obvious any of the other group. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Burden in examining materially different groups having materially different issues also exist.

The requirement is still deemed proper and is therefore made FINAL.

Informalities

The disclosure is objected to because of the following informalities:

2. The specification recites nucleotide sequences, e.g., at pages 27, 28, 45 and 46, however, there are no sequence identifiers "SEQ ID NO:" provided for these sequences. Applicants must comply with the requirements of the sequence rules (37 CFR 1.821-1.825) and provide a paper copy and computer readable form of Sequence Listing containing "all" the sequences. Appropriate correction is required.

3. Fig. 2 (panel A) and Fig. 3 contain letters which are too small to read. Appropriate correction is required.

Claim Objection

4. Claims 1, 2, 10, 17, 21, 23 and 24 are objected to because the claim recites the amino acid and nucleotide sequences using the term "SEQ ID NO.". Use of the term "SEQ ID NO:" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method of modifying a specific acyl-CoA such as 6-CoA or 8-CoA as a substrate (see Fig. 11) by formation of C-O bond, or a method of producing a specific macrotetralide (compounds **1-5**, Fig. 11) using a specific acyl-CoA such as 6-CoA or 8-CoA as a substrate, comprising contacting the substrate with a polypeptide selected from the group consisting of: the polypeptide of SEQ ID NO:3 or 5, and a polypeptide encoded by the nucleotide sequence of SEQ ID NO:1, 2 or 4, does not reasonably provide enablement for a method of modifying a biological

molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide comprised by SEQ ID NO:3 or 5 (read as fragment of SEQ ID NO:3 or 5); a polypeptide encoded by a nucleic acid comprising a nucleotide sequence of SEQ ID NO:1, 2 or 4; and a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation, wherein the biological molecule or the macrotetralide is not identified, and the function of the fragment is not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-18 and 21-25 are directed to a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide comprised by SEQ ID NO:3 or 5; a polypeptide encoded by a nucleic acid comprising a nucleotide sequence of SEQ ID NO:1, 2 or 4; and a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides methods of modifying biological molecules based on the C-O bond formation activities of polypeptides derived from or related to a type II polyketide synthase (PKS) system capable of C-O bond formation, where the C-O bond forming activity of NonJ and NonK, two ketoacyl synthases present within the type II polyketide synthase system (PKS) responsible for biosynthesis of the

macrotetralide nonactin has been identified (page 3). There are no indicia that the present application enables the full scope of the claims in view of the use of the sequences related to NonJ and NonK in the claimed methods as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the polypeptides comprised by SEQ ID NO:3 or 5 (read as fragments); polypeptides encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation; biological molecules as substrates being modified by forming C-O bond; and macrotetralides or macrotetralide analogs to be produced, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification has identified the C-O bond forming activity of NonJ and NonK in nonactin biosynthesis, where NonJ and NonK can act directly on acyl-CoA intermediates in catalyzing C-O bond formation (Fig. 5C), and wherein the amino acid

sequences for NonJ and NonK set forth in SEQ ID NO:3 and 5, respectively; the nucleic acid sequences encoding NonJ and NonK are provided in SEQ ID NO:2 and 4, respectively; and SEQ ID NO:1 sets forth a partial nucleic acid sequence of the nonactin biosynthesis gene cluster including both NonJ and NonK genes; and the use of NonJ and NonK as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8-CoA to produce specific macrotetralides such as compounds **1-5** (Fig. 11; pages 32-49). However, the specification has not demonstrated the use of various biological molecules as substrates except for specific acyl-CoA to produce various macrotetralides, nor has identified any functional fragment of SEQ ID NO:3 or 5, and any functional polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Walczak et al., FEMS Microbiology Letters 183, 171-175 (2000)) teach the isolation and sequencing of 15559 bp of chromosomal DNA of nonactin biosynthsis gene cluster from S. grieseus, and indicates two of the genes, NonK and NonJ are unusual ketoacyl synthase (KAS)α and KASβ homologues. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the use of various biological molecules as substrates, and the identification of functional fragments and related polypeptides of NonK and NonJ, as well as the use of these peptides in the claimed method.

(4). Predictability or unpredictability of the art:

The claims encompass a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide sequence related to NonK or NonJ. However, the use of various biological molecules as substrates and the identification of polypeptide sequence related to NonK or NonJ are not adequately described in the specification, the invention is unpredictable regarding the sequences of functional peptides related to NonK or NonJ.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of modifying a biological molecule by formation of C-O bond, or a method of producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide sequence related to NonK or NonJ. The specification has identified the C-O bond forming activity of NonJ and NonK in nonactin biosynthesis, and the use of NonJ and NonK as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8-CoA to produce specific macrotetralides such as compounds **1-5** (Fig. 11; pages 32-49). However, the specification has not demonstrated the use of various biological molecules as substrates except for specific acyl-CoA to produce various macrotetralides, nor has identified any functional fragment of SEQ ID NO:3 or 5, or any functional polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4. Moreover, there are no working examples demonstrating the use of various biological molecules as substrates and various polypeptide sequence related to NonK or NonJ in the claimed methods. Since the specification does not provide sufficient teachings on identification of functional polypeptide sequence related to NonK or NonJ, and the use of

various biological molecules as substrates, it is necessary to carry out further undue experimentation to identify the functional peptide sequences related to NonK or NonJ, and to use these peptides in the claimed methods.

(6). Nature of the Invention

The scope of the claim encompasses various biological molecules as substrates and various polypeptide sequence related to NonK or NonJ, but the specification does not provide sufficient teachings on the identities and use of these substrate and peptide variants in the claimed methods. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods associated with variants, the teachings in the specification are limited, and the sequences of functional peptides are unpredictable, and therefore, it is necessary to carry out further undue experimentation to identify the functional peptides and use of these peptides in the claimed methods.

6. Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-18 and 21-25 are directed to a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide comprised by SEQ ID NO:3 or 5 (read as fragment); a

polypeptide encoded by a nucleic acid comprising nucleotide sequence of SEQ ID NO:1, 2 or 4; and a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation. While the specification indicates that the instant application has identified the C-O bond forming activity of NonJ and NonK, two ketoacyl synthases present within the type II polyketide synthase system (PKS) responsible for biosynthesis of the macrotetralide nonactin, where NonJ and NonK can act directly on acyl-CoA intermediates in catalyzing C-O bond formation, and wherein the amino acid sequences for NonJ and NonK set forth in SEQ ID NO:3 and 5, respectively; the nucleic acid sequences encoding NonJ and NonK are provided in SEQ ID NO:2 and 4, respectively; and SEQ ID NO:1 sets forth a partial nucleic acid sequence of the nonactin biosynthesis gene cluster including both NonJ and NonK genes (page 3), the specification does not disclose a genus of variants for fragments of SEQ ID NO:3 or 5; polypeptides encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation; biological molecules as substrates being modified by forming C-O bond; and macrotetralides or macrotetralide analogs in the claimed methods. Furthermore, the specification has not identified any fragment of SEQ ID NO:3 and 5 that is functional, and any functional polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4. The use of NonJ and NonK (SEQ ID NO:3 and 5) as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8-CoA to produce specific macrotetralides such as compounds **1-5** (Fig. 11) does not provide written description for a genus of various biological molecules as substrates and various macrotetralides to be produced in the claimed method. Without guidance on

structure to function/activity for fragments of SEQ ID NO:3 or 5 and polypeptides encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4, one skilled in the art would not know how to identify a functional polypeptide. The lack of description on structure to function/activity relationship of NonJ and NonK variant sequences, and the use of these sequences to modify various biological molecules to produce various macrotetralides, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1-18 and 21-25 are indefinite because the claim recites the term "a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:2 (or SEQ ID NO:4)" or "a nucleic acid hybridizing under stringent conditions thereto". The cited term renders the claim indefinite, it is not clear what are these stringent conditions, e.g., are they highly stringent, or with medium or low stringency? Claims 2-9, 11-16, 18, 22 and 24 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

9. Claims 17, 18 and 25 are indefinite because the claim recites the term "(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO:3 or 5". The cited term renders the claim indefinite, it is not clear how a polypeptide can be encoded by an amino acid sequence, since a polypeptide can only be encoded by a nucleotide sequence. Claim 18 is included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which it depends.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
March 16, 2006